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Design and fabrication of phantoms using stereolithography for small-animal imaging systems

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Abstract

Purpose—We have investigated a new technology for fabricating phantoms with fine details for use in small-animal imaging.

Procedures—We used a high-resolution, three-dimensional stereolithography (SL) system to produce performance-evaluation phantoms such as cold-rod Derenzo, hot-channel Derenzo and Defrise phantoms. SL performance was estimated by measuring the dimensions of many structures using a microscope. We also evaluated the degree of water absorption by two different SL resins, Somos® 11120 and Accura® 40, after curing.

Results—The average bias and precision of the cold-rod structures over the size range 0.5 to 1.0 mm, were −0.4 % and 1.74 %, respectively. The water absorption study showed that Somos® 11120 is a more suitable material for nuclear medicine applications.

Conclusion—We have demonstrated that SL is a robust and accurate method for fabrication of phantoms for small animal imaging systems.

Keywords

phantom; Stereolithography; molecular imaging; small-animal imaging; microSPECT; microPET; microMRI; microCT; Quality control

I. INTRODUCTION

In medical imaging and therapy, phantoms are important tools for verifying simulated data, planning radionuclide treatments, and demonstrating the quality of imaging instruments. Small-animal imaging is rapidly becoming an essential tool for preclinical development of new compounds for imaging and therapy. Although imaging performance evaluations and regular quality control are both important, surprisingly, there are relatively few appropriate phantoms available for such procedures. Just as appropriately designed imaging phantoms have played important roles in evaluating the performance of larger systems used for human imaging, we believe that micro-phantoms should be equally important accessories for all serious preclinical imaging research facilities that utilize these modalities. Recently developed high-resolution nuclear medicine imaging systems (e.g., μ SPECT [1], μ PET [2]) require small phantoms with structures having dimensions of less than a millimeter. The techniques used to manufacture these small phantoms should, therefore, be both accurate and precise, ideally to better than 100 μ m. Phantoms for nuclear medicine imaging also generally have fillable compartments, which are more challenging to make when the size is small.

Several mouse-size phantoms are commercially available [3]. However, many μ SPECT and μ PET systems have unique properties that may require custom-designed phantoms with small

structures. For example, the HMS μ SPECT system is a modified triple-head gamma camera (TRIONIX, Twinsburg, OH) equipped with two tungsten pinholes on each head [4]. With 0.8 mm pinholes, the system provides an average resolution of 0.9 mm when the radius of rotation (ROR) is ~ 3 cm. SPECT systems provide their best resolution when an imaging object is as close as possible to the collimator, i.e., a very small radius of rotation is required. Generally, this means that the phantom diameter should be smaller than the SPECT system's ROR, in order to provide adequate clearance between the phantom's outer surface and the front surface of the pinhole or aperture plate.

The main goal of this study was to fabricate phantoms with fine details using stereolithography (SL) [5]. SL is one of the most popular prototyping techniques; it allows the fabrication of accurate three-dimensional (3D) models built from plastic materials, and has been used in many areas of dentistry and medicine, as well as in biomedical science [6-10]. SL creates a plastic part of an arbitrary shape directly from a computer model. Parts are built by photopolymerization when a laser beam is scanned over a liquid resin surface; this converts the liquid into a solid, point-by-point and layer-by-layer. The laser beam is controlled by a computer to build the model. Because some plastic resins used for SL can absorb water, we also investigated the degree of water absorption by two promising SL resin materials, as well as the effect of water absorption on the dimensional stability of the phantoms. Even though SL techniques may also be useful for constructing phantoms for larger, clinical imaging systems, we decided to focus our investigation initially on phantoms for small imaging systems, since larger phantoms can be made reasonably well by conventional machining techniques.

II. METHODS

All phantoms were designed using the computer-aided design (CAD) software, SolidWorks. The output file was converted into a SL readable format, (.stl). A high-resolution, 3D SL system, Viper™ SLA® (3D Systems, CA), was used to build the phantoms. This system is specified to provide a resolution of 75 μ m resolution in the transverse plane and 50 μ m in the vertical direction. A solid state ultraviolet (UV) Nb:YVO₄ laser with a wavelength of 354.7 nm is used in the Viper system. The size of the laser beam was 0.075 ± 0.015 mm, which limits the resolution of the system within each layer. The general procedure for SL phantom manufacturing includes CAD, "printing" of the phantom (automated construction of plastic parts), cleaning of excess resin, and post-build UV curing for approximately 30 minutes to finish curing and hardening the resin.

To test the feasibility of the technique, we fabricated miniature versions of a Derenzo standard quality-control (QC) phantom which is commonly used in nuclear medicine imaging [11]. The Derenzo phantom consists of six pie-shaped wedges each with different rod or channel diameters with center-to-center separation equal to twice their diameter; all six wedge sections are contained within a cylindrical body. We printed rods and channels in a 2 cm long cylinder, 2.4 cm in diameter. The size of the hot channels and cold rods ranged from 0.5 mm to 1 mm. The phantoms were printed from Somos® 11120 resin (DSM Somos, IL), which is optically transparent and has a density close to that of body tissues, 1.12 g/cm³.

The phantom was then scanned using the GE eXplore Locus micro-CT system. We used the highest resolution mode available for the system, 27 μ m. The pixel size in the reconstructed CT image was 0.21 μ m. The CT images were used to examine the appearance of the phantom throughout the whole volume. The cold rods in the Derenzo phantom were then removed and imaged using a microscope to measure their dimensions. DMIRE2 microscope (Leica Microsystems, Germany) and OpenLab software were used for this work. A pre-calibrated conversion factor, 60.48 pixels/100 μ m at 4x magnification, was used to measure the diameter of each rod. We randomly chose 10 rods from each section of the Derenzo phantom for the

diameter measurements. The average and standard deviation over 10 measurements were calculated. The percent difference between the average of the measurements and the originally designed diameter was defined as the bias, and the ratio between the standard deviation and the average size was defined as the precision. We also measured the diameter at five different locations along the axis of the cylindrical rod. This was to check the dimensional uniformity of the fabrication technique, calculated as the percent precision over five measurements along one rod. To check the reproducibility over different phantoms, we fabricated three cold-rod phantoms from the same design and measured their dimensions using the microscope. We defined this reproducibility as the percent precision over three cold rods of each size from the three different phantoms.

Because the phantoms used to test imaging systems usually contain liquids which may remain in the phantom for several days (e.g., for decay of radioactivity), we evaluated the water resistance of two promising resin materials over several days. We printed small cold-rod Derenzo phantoms using the resins, Somos® 11120 and Accura® 40 (3D Systems, CA). The density of Accura® 40 was 1.19 g/cm³. Our initial tests indicated that we should probably use a parylene coating to improve the water resistance of Accura® 40. Therefore, we coated some phantoms with parylene before curing in a UV oven. This coating added less than 20 µm to the rod thickness. After 4 hours, and again after 66 hours of water immersion, we removed the excess water on the surface and measured the weight of each phantom, to compare with its weight before water immersion.

In order to examine imaging performance using several different imaging modalities, we also printed some phantoms in two sizes; one 3-cm-diameter cylindrical phantom had wedges containing rods or channels with diameters ranging from 1.2 to 3.2 mm, in 0.4 mm increments, while the rods or channels in the smaller, 1.8cm-diameter phantom ranged from 0.7 to 1.2 mm in 0.1 mm increments. These Derenzo phantoms were printed using the Accura® 40 resin with parylene coating.

Finally, we also fabricated a long Defrise multiple-disk phantom comprising 26 1.5 mm disks with 1.5 mm spacing. The total length was 8 cm, comparable to the length of a mouse. This phantom is useful for verifying that the spatial resolution and sampling are adequate and uniform along the whole axial field of view [13]. For example, the HMS µSPECT system has an axial field of view of 6 ~ 7 cm, so we can image most of the length of the Defrise phantom with a single rotation of the detectors and no table motion. Unlike some other Defrise phantoms, we designed the disks to be connected using thin walls which extend part of the way around the periphery, instead of using a central support structure; therefore, the center of the phantom is open, allowing a better check of the uniformity of the axial resolution. The Defrise phantom was printed using Somos® 11120 resin, which did not require parylene coating.

It can be challenging to fill very narrow channels in phantoms, due to the surface tension of the liquid. Therefore, to reduce surface tension, we added a few drops of a polysorbate surfactant (Tween® 80 from Aldrich Chemical Co. WI). The amount of Tween was 0.07% by weight in each phantom. The effect of the surfactant on MRI signal intensity was also measured.

Phantoms were imaged using µSPECT, µPET, µCT and/or µMRI. For µSPECT, we used the Harvard Medical School (HMS) system described above, which has an average resolution of 0.9 mm for a 3 cm radius of rotation. Phantoms were filled with ~50 µCi/mL of Tc-99m. All µSPECT images were reconstructed using a 3D-OSEM (ordered-subsets expectation-maximization) algorithm with 20 subsets, 6 projections/subset, and 10 iterations. The voxel size in the reconstructed images was 0.4 × 0.4 × 0.4 mm³. The small-animal CT system we used was the GE eXplore Locus, and we scanned using the 27 µm resolution mode. The CT was performed using 60 kVp and 0.45 mA and a 3-sec exposure for each of 900 views over

360 degrees. No liquid was added to the phantoms for this imaging; the μ CT images were used for visual examination as well as for measurement of structure dimensions. T1- and T2-weighted images were obtained on a Bruker 4.7 Tesla small animal imaging system using a mouse imaging coil; for this imaging, we filled the phantoms with distilled water. T1-weighted images were obtained using a MSME (Multi Slices Multi Echoes) pulse sequence with TE_{eff} of 16.3 ms and TR of 6.7 s. T2-weighted images were obtained using a RARE (Rapid Acquisition with Refocused Echoes) pulse sequence using a TE_{eff} of 70 ms and a TR of 22.3 s. μ PET images were acquired using a Siemens Focus 120 system, which has a nominal resolution of ~ 1.5 mm. We reconstructed μ PET images using Fourier rebinning followed by 2D-OSEM with 16 subsets, 8 projections/subset, and 4 iterations. The reconstructed pixel size and the slice thickness were 0.866 mm and 0.796 mm, respectively.

III. RESULTS

Figure 1 shows some of the Derenzo phantoms we fabricated. All of these inserts were made using the Accura® 40 resin. The 2.4cm-diameter insert in Fig 1(a) has hot channels with sizes ranging from 1.2 mm to 3.3 mm, in 0.4 mm increments. A smaller 1.4-cm-diameter hot-channel insert containing 0.7- 1.2 mm channels is shown in Fig. 1(b). A 1 cm-long cold-rod phantom with 0.7 – 1.2 mm rod diameters (Fig. 1(c)) was also printed. Long rods with such small diameters are difficult to print; therefore, we connected the rods with thin disks as shown in Fig. 1(d) to permit measurement over an extended axial range.

The manufacturing performance of the SL instrument was evaluated by measuring the structure sizes using the microscope described earlier. The CT images demonstrated accurate printing of all Derenzo phantoms. Over the full set of μ CT slices, we confirmed that all channels were open and circular, and all rods/channels were straight. One slice of the μ CT images of the hot-channel phantom made from the Somos® 11120 resin is shown in Fig. 2, with the channel sizes indicated.

Figure 3 shows a digital microscope photograph of one 0.5mm-rod along with the 170 μ m-long calibration bar. The apparent horizontal intensity gradient was caused by the round shape of the rod. The results of the rod dimensional measurements are summarized in Table 1. The average and standard deviation over 10 sample rods were calculated and used for further calculation of percent bias and percent precision. The average bias and precision of the cold-rod structures over all sizes, 0.5 to 1.0 mm, was -0.4% and 1.74% , respectively. The uniformity of the rods was 0.9% and the reproducibility over the phantoms was 1.33% . There were no significant differences in fabrication performance on the basis of measured structure sizes. We believe that these results provide an indication of the excellent performance of the SL technique for small phantom manufacturing.

Cold-rod phantoms fabricated with Somos® 11120 and Accura® 40 were stored in water and their measured weights are listed in Table 2. The phantom made of Accura® 40 had bigger supporting disks, so it weighed more than the Somos® 11120 phantom. Visual inspection confirmed that there were no significant changes in shapes of the rods before and after water immersion. Water absorption by the resins after 4 hours was minimal (0.1 to 0.15% weight change) for both materials; however, after 66 hours in water, the change was greater for Accura® 40 (1.5%) than for Somos® 11120 (0.25%). In addition, the cured Somos® 11120 resin is more transparent than the Accura® 40 resin. For these reasons, Somos® 11120 is a more suitable material for nuclear medicine applications.

Figure 4 shows a slice of the hot-channel phantom images from three different small-animal imaging modalities, (a) μ CT, (b) μ SPECT, and (c) μ PET. In SPECT images all six channel sizes were clearly resolved. With μ PET, five of the six sections were resolved – all except the

1.2 mm channels. The system resolution of the μ PET system is ~ 1.5 mm. The μ CT image demonstrated that all channels were printed correctly.

Images of the 1.8 cm diameter cold-rod Derenzo phantom are shown in Fig 5, (a) μ CT, (b) μ SPECT, and (c) μ MRI. The rod sizes ranged from 0.7 mm to 1.2 mm. The SPECT image shows that the smallest resolvable channel size was 0.8 mm. The CT and MRI images of the phantom shown in Fig. 5(a) and 5(c) demonstrate the excellent fabrication performance of the SL system. The signal intensities in MRI images obtained with and without the surfactant, Tween, differed by less than 5%, both for T1- and T2-weighted images.

An 8 cm-long Defrise phantom was imaged with μ SPECT and μ PET, and the results are shown in Fig. 6. The photograph in Fig. 6(a) shows the axial length of the phantom, and the open central region without a supporting structure. Because all disks were connected with thin walls around part of the periphery, the center of the central coronal slice images in Fig. 6(b) and (c) were not obscured by a support rod, thereby facilitating the evaluation of axial resolution in the axial direction. The SPECT image clearly shows that the useful field of view of the system is ~ 6 cm. However, disks within that FOV were well resolved indicating that there is no significant resolution degradation along the axis. The disks in the PET image of Fig. 6(c) can be resolved over the entire 8 cm axial length, but with worse spatial resolution than seen in the μ SPECT image, and increased noise or artifacts near the ends of the axial FOV.

IV. DISCUSSION AND CONCLUSIONS

We have introduced a new phantom fabrication method based on 3D SL. Micro-phantoms with structures from 0.5 to 3.2 mm in size were printed accurately. The average bias and reproducibility of the cold-rod structures over the size range 0.5 to 1.0 mm, was -0.4% and 1.74% respectively. The reproducibility of the structures between phantoms was 1.33% . The smallest feature we fabricated for the work reported here was 0.5 mm, since our intent was to describe phantoms for small-animal imaging systems, especially for nuclear medicine applications. In a different study, we have shown that the smallest wall thickness that can be fabricated reliably and consistently was $150\ \mu\text{m}$ [14]. The water resistance of the resin material was also satisfactory, which implies that SL resins, especially Somos® 11120, can be used for long acquisition conditions in nuclear medicine. Water absorption by the resins after 4 hours was minimal (0.1 to 0.15% weight change) for both materials; however, after 66 hours in water, the change was greater for Accura® 40 (1.5%) than for Somos® 11120 (0.25%). This may not provide guidance for making phantoms to hold long-lived radionuclides, e.g., Ge-68, since water absorption has not yet been tested for these resins over longer periods of time. The flexibility of the CAD/SL construction process implies that other custom designs can also be fabricated, using one of many available resins. We have also shown that SL technology can be used to fabricate phantoms with inner components that are smaller than those currently available from commercial vendors. For example, the size of the smallest feature in the Data Spectrum ultra-micro-hot spot phantom [3] is 0.75 mm, and a cold-rod version of that phantom is not even available.

The fabrication technique we evaluated here can help researchers build phantoms like these and others to (1) determine the physical performance of their individual imaging systems, as well as the accuracy and precision of spatial registration across multiple modalities, (2) assess the stability of imaging characteristics over time, including MRI signal strengths, allowing staff to perform appropriate repairs or calibration procedures to maintain a high level of quality control, and (3) evaluate performance in prototypical tumor detection and/or quantitation tasks, thereby enabling prediction of useful performance characteristics, such as the minimum tumor-to-background contrast required to accomplish particular imaging tasks in realistic mouse phantoms. Measurements like these will permit developers of new contrast agents,

radiopharmaceuticals and other compounds for cancer diagnosis or therapy to understand -- even in advance of animal imaging studies -- the target specificity that will ultimately be required to achieve success in a given imaging application.

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Figure 1.

Photographs of some of the phantoms we fabricated, (a) a small hot-channel, (b) a smaller hot-channel, (c) a short cold-rod, and (d) a long cold rod phantom.

Figure 2.
μCT image of hot-channel phantom with channel sizes, 0.5 ~ 1.0 mm, made using the Somos® 11120.

Figure 3.
An image of a 0.5 mm cold-rod taken by a microscope. The white horizontal line indicates the width of the rod. All the size measurements were based on images from the microscope.

Figure 4. Transaxial images of a hot-channel phantom obtained with (a) μ CT, (b) μ SPECT, and (c) μ PET. The channel sizes ranged from 1.2 mm to 3.2 mm, in 0.4 mm increments. The outer diameter of the cylinder was 2.4 cm.

Figure 5. Transaxial images of the smaller cold-rod phantom with (a) μ CT, (b) μ SPECT and (c) μ MRI. The channel sizes ranged from 0.7 mm to 1.2 mm, in 0.1 mm increments. The outer diameter of the cylinder was 1.8 cm.

Figure 6. Images of Defrise phantom; (a) photograph, (b) μ SPECT, and (c) μ PET. The total length was 8 cm and the disk thickness was 1.5 mm.

Table1
Performance of SL technique measured using a microscope

Size (mm)	A cold-rod phantom			Reproducibility across three cold-rod phantoms (%)
	Bias (%)	Precision (%)	Uniformity (%)	
0.5	-1.21	2.67	0.97	1.16
0.6	-1.62	1.66	1.18	2.35
0.7	-0.46	2.35	0.98	1.30
0.8	-0.07	0.81	0.81	1.20
0.9	0.85	1.61	0.71	1.21
1.0	0.11	1.31	0.76	0.74
Average	-0.40	1.74	0.90	1.33

Table 2
Weight of cold-rod phantoms made of different materials before and after storing in water

	Accura® 40	Somos® 11120
Before	4.360 g	2.339 g
After 4 hours (% change)	4.366 g (+0.16 %)	2.341 g (+0.11 %)
After 66 hours (% change)	4.424 g (+1.90 %)	2.344 g (+0.21 %)